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(54) Title: USE OF VALERIANA FOR THE TREATMENT OF RESTLESS LEG SYNDROME AND RELATED DISORDERS

(57) Abstract

A novel method of inhibiting at least one symptomology of Restless Leg Syndrome (RLS) and its related disorders, including disorders such as periodic limb movements in sleep (PLMS) and periodic limb movement disorder (PLMD), is disclosed. Said method optionally comprising identifying a host, preferably a human, afflicted with Restless Leg Syndrome (RLS) and its related disorders; and comprising administering to said host a pharmaceutically effective amount of *Valeriana*, preferably an extract of *Valeriana*. A novel method of inhibiting at least one symptomology of Restless Leg Syndrome (RLS) and its related disorders is disclosed. The method may also be used to treat a host in order to diminish undesired limb movements, and may involve the administration of a particular compound, found in the above-mentioned extracts, preferably selected from the group consisting of 10(14)-Aromadendren-4-ol, 6,10(14)-Guaiadien-4-ol, Valerenal, Valerenol, Valerenic acid, Acetoxyvalerenic acid, Hydroxyvalerenic acid, mimetics thereof, and may involve the administration of a combinations of these particular compounds and mimetics thereof.

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USE OF *VALERIANA* FOR THE TREATMENT OF RESTLESS LEG SYNDROME AND RELATED DISORDERSBackground of the InventionField of the Invention

This invention relates to novel methods for treating Restless Leg Syndrome (RLS) and related disorders, such as periodic limb movements in sleep (PLMS) and periodic limb movement disorder (PLMD), and for diminishing the occurrence of unwanted limb movements. Particularly, this invention relates to the use of *Valeriana*, and more particularly to an extract of *Valeriana officinalis* L., for diminishing the occurrence of unwanted limb movements, either associated with or unassociated with RLS and/or related disorders.

Description of the Related Art

The set of conditions known as Restless Leg Syndrome (RLS), also known as Ekbom's Syndrome following Ekbom's description of the syndrome in 1944, has been known since at least 1685 (Willis). RLS is a fairly common sensorimotor disorder, yet is not widely recognized by the medical profession or healthcare providers. It is characterized in that it typically gives the individual who suffers from RLS an unpleasant sensation in the legs at rest, causing what is often described as an irresistible desire to move, which generally alleviates the discomfort. (Jones and Deodra, 1997) Also typically, individuals afflicted with RLS experience indescribable crawling sensations in their legs that often occur at night and that are only relieved by moving the legs. (Boucher, 1997) Accordingly, RLS and its related disorders are thought to be a common cause of severe insomnia. (Fox, 1986) RLS is idiopathic in most patients, and has been identified as a presenting feature of iron deficiency, and is also common in uremia, pregnancy, diabetes mellitus, rheumatoid arthritis, and polyneuropathy. (O'Keeffe, 1996) PLMD and PLMS, disorders related to RLS, are characterized by episodes of jerking of the limbs, often during periods in which the individual is asleep, and sometimes during periods in which the individual is awake.

RLS affects millions of individuals, having an estimated prevalence of between 1% and 5%. (Wetter and Pollmacher, 1997) Indeed, at least mild symptoms of RLS have been reported to occur in up to 5% of the population of the United States. (O'Keeffe, 1996)

The formal criteria for diagnosis of RLS include: (i) symmetric or asymmetric dysesthesias of the lower, and sometimes also of the upper, extremities; (ii) dysesthesia are typically present at rest, and are especially prevalent at night; (iii) dysesthesia induce a need to move; (iv) movement gives relief, but only for a few seconds. Occasionally, the dysesthesia may be painful. Additional criteria include: (v) involuntary, rhythmic retraction movements occurring especially at night, and especially during sleep stages I and II; (vi) sleep is disrupted and superficial, followed by daytime fatigue. (Grandjean, 1997) Thus, clinical criteria for diagnosis include sleep disturbance, involuntary movements in sleep or wakefulness, a normal neurologic examination, a chronic clinical course, and, in some cases, a positive family history. (Trenkwalder et al., 1996) And the following four minimal criteria for diagnosis have been proposed: (1) desire to move the extremities, often associated with paresthesias/dysesthesias; (2) motor restlessness; (3) worsening of symptoms at rest with at least temporary relief by activity, and (4) worsening of symptoms in the evening or night. (Walters, 1995) The related disorders share some of these characteristics.

The underlying cause of RLS and its related disorders is not clearly known. However, it has been observed that the frequency of occurrence increases with advancing age. In most individuals with RLS, the results of complete blood cell counts and iron, ferritin, folate, and vitamin B12 levels are normal. No hematologic or chemical abnormalities are associated with individuals who experience periodic movements during sleep who also do not have RLS (Krueger, 1990).

Regarding the etiology of RLS and related disorders, pathophysiologically it has been reported that a malfunction of dopamine and opiate receptors in the central nervous system are associated with RLS and related disorders. (Grandjean, 1997) And while the precise aetiology of RLS and PLMS are unknown, it has been reported that periodic leg movements result from a suprasegmental disinhibition of descending inhibitory pathways. An evaluation of the efficacy of certain drugs revealed that, according to one study, the dopaminergic, adrenergic and opiate systems play a major role in the pathogenesis of RLS/PLMS. In spite of this association, therapy of RLS and PLMS remains symptomatic except for some secondary forms. (Wetter and Pollmacher, 1997) Indeed, one study has reported that “[w]hile the Dopamenergic CNS pathways have been thought to be the primary neurotransmitter involved, the opioids secondary, there is mounting evidence that the situation is far more complicated, that many neurotransmitters, including stimulating and inhibiting amino acids, play a part.” (Williams, 1996)

Currently, RLS is typically treated by drugs such as clonazepam, narcotics, dopamine agonists, benzodiazepines, clonidine, gabepentin, (Joy, 1997; Wetter and Pollmacher, 1997; Trenkwalder et al., 1996) and magnesium (Hornyak et al., 1998), and typically via oral administration. Currently, one popular pharmaceutical treatment of RLS in the United States is pramipexole, known by the trade name Mirapex, [available from Pharmacia and Upjohn] which has been reported to cause major side effects including insomnia, and dizziness. For example: “In pramipexole recipients with early disease, the most commonly experienced adverse events were nausea, dizziness, somnolence, insomnia, constipation, asthenia and hallucinations.” (Dooley M, Markham A, Pramipexole. A review of its use in the management of early and advanced Parkinson's disease, *Drugs Aging* 1998 Jun;12(6):495-514); “The most common adverse events (< 10%) were dizziness, insomnia, nausea, and postural hypotension.” (Wermuth L, A double-blind, placebo-controlled, randomized, multi-center study of pramipexole in advanced Parkinson's disease, *Eur J Neurol* 1998 May;5(3):235-242); “In the assessment of adverse events, nausea, insomnia, constipation, somnolence, and visual hallucinations occurred more frequently in the pramipexole treatment group compared with placebo patients.” (Shannon KM, Bennett JP Jr, Friedman JH, Efficacy of pramipexole, a novel dopamine agonist, as monotherapy in mild to moderate Parkinson's disease. The Pramipexole Study Group. *Neurology* 1997 Sep;49(3):724-8).

Therefore, there exists a need for an effective, alternative treatment and related treatment regime options for individuals who are afflicted with RLS and/or its related disorders. More particularly, there exists a need for treatments that do not induce the unwanted effects observed in modern therapeutics for Restless Leg Syndrome (RLS) and related disorders.

Summary of the Invention

A novel method of inhibiting at least one symptomology of Restless Leg Syndrome (RLS) and its related disorders is disclosed. Said method comprises identifying a host afflicted with Restless Leg Syndrome (RLS) or a

related disorder; and administering to said host a pharmaceutically effective amount of *Valeriana*. The *Valeriana* is preferably an extract, and more preferably an extract of *Valeriana officinalis* L. The host is preferably a mammal, and may also preferably be a canine, feline, or member of the Class Rodentia. Methods of the invention may be used to treat a host in order to diminish undesired limb movements, and may involve the administration of a particular compound, found in the above-mentioned extracts, preferably selected from the group consisting of 10(14)-Aromadendren-4-ol, 6,10(14)-Guaiadien-4-ol, Valerenal, Valerenol, Valerenic acid, Acetoxyvalerenic acid, Hydroxyvalerenic acid, and mimetics thereof, and may involve the administration of a combinations of these particular compounds and mimetics thereof.

Brief Description of the Drawings

The accompanying drawings, which are incorporated in and form part of the specification, merely illustrate embodiments of the present invention. Together with the remainder of the specification, they are meant to serve to explain the principles of the invention to those of skill in the art. In the drawings:

FIG. 1 illustrates a graphic depiction of the effect of commercially available Valerian extracts on binding to the *peripheral* benzodiazepine receptors according to the invention.

FIG. 2 illustrates a graphic depiction of the lack of effect of commercially available Valerian extracts on binding to the *central* benzodiazepine receptors according to the invention.

FIG. 3 illustrates a schematic Valerian fraction flow diagram including an exemplary isolation scheme used to assay dopamine D3 receptor binding activity.

FIG. 4 illustrates the chemical structures of five structurally related compounds determined to be active in a dopamine D3 bio-assay according to the invention.

FIG. 5 illustrates the inhibition of ligand binding to the human dopamine receptor by various compounds isolated from Valerian according to the invention.

Detailed Description of the Preferred Embodiment

In a preferred embodiment, a natural plant extract is provided, and particularly an extract of *Valeriana*, and more particularly an extract from *Valeriana officinalis* L., that affects the peripheral and central nervous system in a manner that alleviates the symptomologies of Restless Leg Syndrome (RLS) and related disorders. Further, the invention provides the advantage of alleviating the symptomologies of RLS and related disorders without causing the side effects associated with benzodiazepine-type treatment, and other current treatment or treatments of, RLS and related disorders. The invention provides the advantage of providing an alternative treatment option for RLS and related disorders, of which there is a need in the art.

Another advantage of the invention, which may include the use of Valerian extract in the treatment of RLS and related disorders, is that extracts of *Valeriana* have not been shown to cause such side effects and therefore, the treatment of RLS with *Valeriana* may increase compliance for the RLS patient as well as address the specific problem of insomnia associated with RLS and/or other pharmaceutical treatments for RLS. These current treatments have a wide variety of negative side effects, which have been reported and detailed (Silber, 1997). Also, tolerance to the treatment can develop, causing the efficacy of a particular treatment regime to diminish with time. Also, rebound

phenomena are associated with currently known treatments (Krueger, 1990; Hornyak et al., 1998). Additionally, and as would be appreciated by one skilled in the art, current treatments such as benzodiazepines are associated with a host of unwanted effects such as memory loss, addiction potential, and other related side effects.

As used herein, the terms "*Valeriana*" and "valerian" each refer to any plant of the Valerianaceae, and therefore refers, at least to, the plant designated *Valeriana officinalis* L. This species includes all recognized subspecies of *Valeriana officinalis* L. Some of these subspecies are also commonly referred to, in alternative taxonomic systems, as: *Valeriana exaltata* J.C. Mikan, *Valeriana nitida* Kreyer, *Valeriana palustris* Wibel, *Valeriana wolgenis* Kazak, *Valeriana grossheimii* Vorosch, *Valeriana collina* Wallr, *Valeriana Rossica* P.A. Smirn, *Valeriana spryngini* P.S. Smirn, *Valeriana angustifolia* Tausch, *Valeriana tenuifolia* Vahl, *Valeriana wallrothii* Kreyer, *Valeriana ucrainica* Demjan, *Valeriana sambucifolia* J.C. Mikan, *Valeriana excelsa* Poir, and *Valeriana officinalis* L. subsp. *excelsa* (Poir.) Rouy. Plants of the species *Valeriana officinalis* L. may be characterized as follows: These plants grow from a short rhizome to 2 m high, flowers, and then die back again in the winter. These plants have pinnately-divided leaves with six to ten pairs of lance-shaped leaflets, and bear many small white or pink flowers in a dense head of several stalked clusters. The heads bare small (5 mm) tapered seeds.

As used herein, the term "root" or "roots" refers to all of subterranean portion of a specifically or generically identified plant, including, but not limited to, the roots, the rhizomes, and the stolons of the specifically or generically identified plant. Where the term "roots" is not modified by a specifically or generically identified plant, it will be understood that the term refers to the roots of the genus, and the various species, of *Valeriana*.

As used herein the term "Restless Leg Syndrome (RLS) and related disorders" means diseases, disorders, syndromes or conditions characterized by periodic limb movements such as periodic limb movements such as in sleep (PLMS) and periodic limb movement disorder (PLMD), and the treatment of such diseases, disorders, syndromes or conditions includes any pharmacological means of diminishing the occurrence of unwanted limb movements.

As used herein, the terms "reduces," "reduced," or "reducing," when used to refer to one or more symptomatology of a disease, refers to any observable lessening of that characteristic when the method or composition of the invention is compared to prior art methods or compositions.

As used herein, the terms "disorder" and "disease" refer to any disorder, disease, condition, syndrome or combination of manifestations or symptoms recognized or diagnosed as a disorder. If modified by reference to a particular disease or by reference one or more or a set of manifestations or symptoms, that usage of "disorder" or "disease" refers to any such disorder, disease, condition, syndrome or combination of such manifestations or symptoms recognized or diagnosed as a such disorder.

As used herein, the term "pharmaceutically effective amount" refers to an amount sufficient to alleviate, in any degree or manner, one or more of the manifestations or symptoms recognized or diagnosed as associated with the modifying disorder, the modifying manifestations, or the modifying symptom.

EXAMPLE 1

EFFECTS OF VALERIAN EXTRACT ON PERIPHERAL AND CENTRAL NERVOUS SYSTEM

In Table 1, data are shown which demonstrate that an extract from *Valeriana officinalis* L. affected the peripheral and central nervous system in a manner consistent with alleviating one or more of the symptomologies of Restless Leg Syndrome (RLS) and related disorders. All bio-assays, except the Rat A1, were performed at the following laboratory according to standard methods known to those skilled in the art:

Panlabs Taiwan, Ltd.

158 Li-Teh Road, Peitou

Taipei, Taiwan

R.O.C.

Two examples of suitable assay procedures are as follows:

Human D3 Assay: This assay measures binding of [³H]-Spiperone to human dopamine D3 receptors. CHO cells stably transfected with a plasmid encoding the human dopamine D3 receptor were used to prepare membranes in modified Tris-HCl pH 7.4 buffer using standard techniques. A 10 mg aliquot of membrane was incubated with 2 nM [³H]-Spiperone for 120 minutes at 37°C. Non-specific binding was estimated in the presence of 25 μ M S-(-)-sulpiride. Membranes were filtered and washed three times and the filters are counted to determine the amount of [³H]-Spiperone specifically bound. Compounds were screened at 10 μ M.

Human A1 Assay: This assay measures binding of [³H]-DPCPX to adenosine A1 receptors. CHO cells stably transfected with a plasmid encoding the human adenosine A1 receptor were used to prepare membranes in modified HEPES pH 7.4 using standard techniques. A 10 mg aliquot of membrane was incubated with 1 nM [³H]-DPCPX for 90 minutes at 25°C. Non-specific binding was estimated in the presence of 100 μ M R(-)-PIA. Membranes were filtered and washed three times and the filters were counted to determine [³H]-DPCPX specifically bound. Compounds were screened at 10 μ M.

Rat adenosine A1 receptor binding assays were performed at the following laboratory according to standard methods known to those skilled in the art:

Oceanix Biosciences

7170 Standard Drive

Hanover, MD 21076

Rat A1 Assay: This assay measures binding of [³H]-8-Cyclopentyl-1,3-dipropylxanthine to adenosine A1 receptors. Rat cortical membranes, prepared using standard techniques, were used as a source of the receptor. Reactions were carried out in 50 mM TRIS-HCl (pH 7.7) for 60 minutes at 25°C. Non-specific binding was estimated in the presence of 10 μ M 2-chloroadenosine. The reaction was terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters was determined and compared to control values in order to ascertain any interactions of test compound with the adenosine A1 binding site.

It has further been demonstrated, through *in vitro* binding tests, that extracts of *Valeriana officinalis* L., produced according to the method described in U.S. Patent Application Ser. No. 09/358,375, filed July 21, 1999, and

entitled "Process for the Extraction of Valerian Root," the entire contents of which are incorporated herein by reference, favorably interact with certain Central Nervous System (CNS) receptors, for example, the GABA, Adenosine, and Dopamine receptors. Such bind would explain the calming action of said extracts (see Table 1). In contrast, the CNS binding site associated with benzodiazepines was not affected by said Valerian extracts (see Figures 1 and 2). The results depicted in Figure 2 indicate, via an *in vitro* model, that extracts of *Valeriana officinalis* L. will not result in the problematic side effects and side effect profiles associated with currently available benzodiazepine-type drugs. Additionally, as demonstrated by the data depicted in Figure 1, extracts of *Valeriana officinalis* affect the binding of *peripheral* benzodiazepine receptors. Thus, is it believed, although the invention is not limited by any theory or hypothesis, that the peripheral benzodiazepine receptors mediate the activity of mitochondria in muscle cells, and thereby effect muscle activity (see Figures 1 and 2), and therefore mediate muscle calming.

Table 1. Percent Inhibition of Various Extract Fractions Against Various Receptors

	% Inhibition							Mean	SD
	VRE.001	VRE.002	VRE.003	VRE.004	VRE.005	VRE.006	RE.007		
A1 Human									
0.1 mg/mL	-10	-9	17	14	-12	-9	8	-0.14	12.62
1 mg/mL	38	-9	60	47	28	32	23	31.29	21.68
A1 Rat									
0.1 mg/mL	43.85	12.64	11.36	28.45	21.86	20.57	22.76	23.07	10.91
1 mg/mL	84.69	-7.28	47.93	76.01	60.56	42.77	52.81	51.07	29.80
BDZ Central									
0.1 mg/mL	13.08	3.32	19.23	13.01	-1.9	16.4	8.26	10.20	7.46
1 mg/mL	-42.73	-11.31	19.61	-31.61	-13.73	6.57	13.98	-8.46	23.32
BDZ Peri									
0.1 mg/mL	38.83	2.32	55.5	41.86	14.66	12.63	21.19	26.71	19.04
1 mg/mL	83.64	17.82	83.85	73.33	75.71	70.84	71.73	68.13	22.82
Cl Channel									
0.1 mg/mL	12.58	-33.05	11.7	3.81	1.79	9.45	-6.09	0.03	15.98
1 mg/mL	98.15	14.66	40.02	86.72	91.95	49.34	10.46	55.90	36.73

		% Inhibition								
		VRE.001	VRE.002	VRE.003	VRE.004	VRE.005	VRE.006	RE.007	Mean	SD
D1										
0.1 mg/mL	13.52	24.52	43	8.95	5.36	37.64	14.48	21.07	14.50	
1 mg/mL	70.25	34.88	37.78	36.55	68.16	49.22	23.44	45.75	17.69	
GABA-A										
0.1 mg/mL	94.5	61.56	83.24	91.89	90.49	89.53	36.16	78.20	21.61	
1 mg/mL	93.24	95.62	97.56	91.37	100.13	96.79	59.73	90.63	13.92	
GABA-B										
0.01mg/mL	26	13	-10	46	12	7	-6	12.57	19.08	
0.1 mg/mL	82	14	28	66	77	53	4	46.29	31.14	
1 mg/mL	102	96	81	116	105	110	48	94.00	23.14	

EXAMPLE 2

PROCESS FOR PREPARING A VALERIAN EXTRACT

As a further non-limiting, preferred example, an extract of the plant *Valeriana officinalis* and specifically, of its roots, wherein the amount of valepotriates in the extract is reduced below a detectable level, may be obtained, in a manner consistent with that described in U.S. Patent Application Ser. No. 09/358,375, filed July 21, 1999, and entitled "Process for the Extraction of Valerian Root," the entire contents of which are herein incorporated by reference, by performing the follow steps, in the following sequence. As will be appreciated by those of skill in the art, such a process yields an extract possessing the following compounds as constituents: 10(14)-Aromadendren-4-ol, 6,10(14)-Guaiadien-4-ol, Valerenal, Valerenol, Valerenic acid, Acetoxyvalerenic acid, Hydroxyvalerenic acid. Additionally, mimetics of these constituents will possess certain similar biological properties as the identified constituents, and combinations of these constituents, including combination of these constituents and mimetics thereof, may be employed within the meaning of the invention.

(1) At an extraction facility the *Valeriana officinalis* L. rhizome, roots, and stolons (Valerian biomass) are prepared for extraction by chipping in a hammermill with an appropriate screen installed for sizing. The chipped Valerian biomass is analyzed to ensure that at least 85% passes through a Tyler 20-mesh screen. The chipped Valerian biomass is packaged in a polyethylene container, doubly lined with polyethylene bags, and closed with a polyethylene lid.

(2) The chipped Valerian biomass is added to an extraction solvent in a ratio of 1 kg of chipped Valerian biomass to 5L of extraction solvent, then stirred. The extraction solvent consists of a mixture of 70% denatured ethanol (95% ethanol + 5% methanol) and 30% potable water by volume. The mixture is stirred and heated to reflux (77-80°C) for at least 5, or approximately 6, 7, 8, or 10 hours to reduce the levels of valepotriates by a target of not less than 95% from the level initially found in the extraction mixture, and to a low as undetectable levels. The mixture

is cooled below reflux (approximately 40-50°C, or more particularly 42, 45, and 47°C) and the solids are filtered from the liquid. The extraction vessel and the solids in the filter are rinsed with the same solvent solution as used for extraction. The rinse consists of 2 L of solvent solution for each 1 kg of chipped Valerian biomass extracted. The filtrate containing the extracted material is concentrated to an oily consistency under reduced pressure at approximately 50°C, or approximately 45°C or 55°C, to a final volume of approximately 0.16L for each 1 kg of chipped Valerian root extracted.

(3) Optionally, the concentrate is mixed with an acceptable chemical base, to reduce the odor of the extract, as described in U.S. Patent Application Ser. No. 60/173,983, entitled "Process For The Reducing The Odor of *Valeriana*," and filed herewith, the entire contents of which are hereby incorporated by reference herein.

(4) The concentrate is mixed with an excipient (maltodextrin) to facilitate drying. The final maltodextrin concentration by weight will be between 20 – 25% of the botanical drug substance.

(5) The mixture of concentrate and excipient is dried under a reduced pressure of 28-30 inches Hg, gauge, and a temperature of 40-50°C, or more particularly 42, 45, and 47°C, until the water content is 5% or less, or 10% or less, or 2.5% or less, by Karl Fisher analysis. The dried extract on excipient is milled to a target of 90% passing through an 80-mesh screen.

(6) The final powder is packaged in 60 L capacity containers constructed of High Density Polyethylene (HDPE). The containers are double lined with Low Density Polyethylene (LDPE) bags that contain no dye and are extruded from virgin polymer only. Twisting the excess bag closed at the open end and securing it with an elastic band closes each bag within the packaging container. These containers have a HDPE lid with a gasket seal to the container. The lid is secured to the container with an aluminum clamp band. The clamp band is secured with a non-removable security seal.

Said extract, or other extracts of *Valeriana*, obtained via methods that are appreciated by those skilled in the art, are administered to a host, said host having been identified as afflicted with Restless Leg Syndrome and related disorders, in a pharmaceutically effective amount.

Furthermore, said extract, or other extracts of *Valeriana*, obtained via the above-described method may be, as will be appreciated by those skilled in the art, administered to a host, preferably a mammalian host, and most preferably a canine, a feline, a rodent, (include a murine), or a human host, said host having been identified as suffering from or afflicted with undesired limb movements associated with Restless Leg Syndrome (RLS) or a related disorder. As will be appreciated by those of skill in the art, the above-described extract is preferably delivered in a pharmaceutically effective amount that does not induce unwanted side effects

The extract produced, and preferably the tablets produced according to the methods of the invention advantageously may be administered to an individual in a dose containing a pharmaceutically-effective amount of Valerian, Valerian extract, or component(s) therein. This administration can be through any effective route. It is contemplated that administration may be effected, for example, preferably orally, but also may also be administered intramuscularly, subcutaneously, intraperitoneally, transdermally, transmucosally, buccally, or through inhalation or pulmonary infusion. Dosages that are contemplated for a 70 kg adult human range from a lower limit of 10, 25, 50,

100, 150, 200, or 250 mg to an upper limit of 750, 1000, 1500, 2000, 2500, 3000, 4000, 5000, or up to 10,000 mg. of the compositions described herein, or other extracts of valerian. Preferred dosages for a 70 kg human are from about 100, 200, or 250 mg to about 1000, 1500, 2000, or 2500 mg. These dosages can be administered once, twice or up to four times per day, or two or more dosages may be combined. The dose may also be tailored to achieve a desired effect, but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

The invention may also encompass pharmaceutical compositions comprising a pharmaceutically acceptable carrier prepared for storage and subsequent administration, which have a pharmaceutically effective amount of the extract disclosed above in a pharmaceutically acceptable carrier or diluent. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A.R. Gennaro edit. 1985). Preservatives, stabilizers, dyes and even flavoring agents may be provided in the pharmaceutical composition. For example, sodium benzoate, sorbic acid and esters of p-hydroxybenzoic acid may be added as preservatives. In addition, antioxidants and suspending agents may be used.

These compositions may be formulated and used as, preferably, tablets, and also as capsules for oral administration. Suitable additional excipients are, for example, water, saline, dextrose, mannitol, lactose, lecithin, albumin, sodium glutamate, cysteine hydrochloride, and the like. In addition, if desired, the pharmaceutical compositions may contain relatively small amounts of nontoxic auxiliary substances, such as wetting agents, pH buffering agents, and the like.

In practicing the compositions of the invention, the formulated dosage may be used alone or in combination with other therapeutic or diagnostic agents. These products can be utilized *in vivo*, ordinarily in a mammal, preferably in a human, or *in vitro*. In employing them *in vivo*, the products or compositions can be administered to the mammal in any of a variety of manners known to persons skilled in the art, and may employ any of a variety of dosage forms.

EXAMPLE 3

INTERACTION OF VALERIAN ROOT EXTRACTS AND FRACTIONS OF VALERIAN ROOT EXTRACT WITH HUMAN DOPAMINE D3 RECEPTORS

It has also been discovered that Valerian extracts demonstrate specificity for the Dopamine D3 subtype versus the other Dopamine receptors. Without being bound to a particular theory or action or functional hypothesis, it is believed that Mirapex (pramipexole), noted above, acts on the D3, D2, D4 receptor subtypes, and that Valerian's relative selectivity for the D3 subtype may be responsible for Valerian's lower incidence of side-effects relative to Mirapex.

Table 2. Effect of Valerian on ligand binding to human recombinant dopamine receptors. (The ligand used was ^3H -SCH-23390 in the dopamine D₁ assay and ^3H -Spiperone in all other assays.)

Receptor	Assay #	N =	Conc. $\mu\text{g/mL}$	% Inhibition
Dopamine D ₁	1	2	1000	36
	1	2	100	-8
	1	2	10	-2
		2	1000	69
Dopamine D _{2L}	1	2	1000	19
	1	2	100	2
	1	2	10	-10
Dopamine D _{2S}	1	2	1000	26
	1	2	100	-2
	1	2	10	6
Dopamine D ₃	1	2	1000	77
	1	2	100	13
	1	2	10	6
	2	4	2000	82
	2	4	1000	49
	2	4	500	24
	2	4	250	17
	2	4	125	6
	2	4	62.5	7
	2	4	31.25	4
Dopamine D _{4,2}	1	2	1000	19
Dopamine D _{4,4}	1	2	1000	-15
	1	2	100	-8
	1	2	10	10
Dopamine D _{4,7}	1	2	1000	0

This example demonstrates the interaction of Valerian and fractions prepared from Valerian with human dopamine D3 receptors *in vitro*.

Low doses of dopamine D3 receptor agonists have been shown to increase slow wave sleep (SWS) and rapid eye movement (REM) sleep in animal models. Dopamine D3 agonists also reduce locomotor activity in rats. Studies indicate that treatment with a specific D3 agonist does not directly induce the release of dopamine. This suggests that the direct interaction of agonists with the dopamine D3 receptor is involved in the induction of sleep.

Aqueous and hydroalcoholic extracts of *Valeriana officinalis* L. (valerian) roots are commonly used as sedative agents. To understand the mechanism of this pharmacological activity, we investigated the effect of Valerian on ligand binding to the human dopamine D3 receptor. Fractions prepared from such extracts were also tested for interaction with dopamine D3 receptors to identify individual compounds, or classes of compounds, that may be partially responsible for the sedative action of Valerian.

Materials and methods used in performing this example were as follows:

Valerian was subjected to the fractionation scheme schematically depicted in Figure 4.

As the source of, and to isolate the receptors used in the example, membranes prepared from Chinese hamster ovarian (CHO) cells, stably transfected with a plasmid encoding the human dopamine D3 receptor, were used.

Sample preparation: Stock solutions of the valerian root extract were prepared by dissolving in 50% ethanol/water followed by sonication and filtration (0.45 μ m) or by dissolving in 100% DMSO. Valerian fractions were dissolved in 100% DMSO. Prior to analysis, stock solutions were diluted in appropriate buffer. In each assay, the final ethanol or DMSO concentration was less than or equal to 1%.

Receptor binding assays: Standard receptor binding assays were performed at the following analytical laboratory: Panlabs Taiwan, Ltd., 158 Li-Teh Road, Peitou, Taipei, Taiwan, R.O.C. The assay method, based on the assay described in Sokoloff, P., Giros, B., Martres, M.-P., Bouthenet, M.-L. and Schwartz, J.-C. Molecular cloning and characterization of a novel dopamine receptor (D3) as a target for neuroleptics. *Nature* 347: 146-151, (1990), was as follows: The assay measures binding of [³H]Spiperone to human dopamine D3 receptors. CHO cells stably transfected with a plasmid encoding the human dopamine D3 receptor are used to prepare membranes in modified Tris-HCl pH 7.4 buffer using standard techniques. A 10 mg aliquot of membrane is incubated with 2 nM [³H]-Spiperone for 120 minutes at 37 °C. Non-specific binding is estimated in the presence of 25 μ M S-(*l*)-sulpiride. Membranes are filtered and washed 3 times and the filters are counted to determine [³H]-Spiperone specifically bound. Compounds are screened at 10 μ M. Results were as follows: K_d = 0.12 nM; B_{max} = 1.9 pmol/mg protein; Specific Binding = 85%.

The Reference Data were as depicted in the following table, Table 3:

Table 3. Reference Data For Receptor Binding Assay

Reference Data:	Compound	IC ₅₀ (nM)	K _i (nM)	nH
	R-(<i>l</i>)-Apomorphine	270	15	0.9
	(+)-Butaclamol	13	0.73	1.0
	Chlorpromazine	38	2.1	0.9
	Clozapine	4,200	240	1.0
	Dopamine	1,100	64	0.9
	c/s-Flupenthixol	0.83	0.047	0.9
	Haloperidol	26	1.5	1.2
	SCH-23390	> 10,000	-	-
	SKF-38393	> 10,000	-	-
	*Spiperone	0.7	0.04	1.0
	S-(<i>l</i>)-Sulpiride	850	48	1.0

*Indicates standard reference agent used.

SCH-23390 = 7-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-7H-3-benzazepine-7-ol;

SKF-38393 = 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-7H-3-benzazepine HCl

Valerian root extract has been reported to possess sedative activity, presumably through the interaction of one or more of its constituents with receptors mediating sedation. The neuromodulator, dopamine, is a suspected

sleep-inducing factor through its specific interaction with dopamine receptors. While there are a number of known dopamine receptor subtypes, activation of the dopamine D3 receptor is most closely associated with dopamine's sleep-inducing and sedative effects. This has been demonstrated with agents that selectively activate the D3 receptor. Studies indicate D3 selective agonists induce both slow wave sleep (SWS) and rapid eye movement (REM) sleep in rats.

To understand Valerian's mechanism of action, Valerian was tested in this example for its ability to displace radio-labeled ligand (^3H -spiperone) from the human dopamine D3 receptor *in vitro*. The data from the testing of Valerian at various concentrations on different days is summarized below in Table 4. The results indicate that Valerian root extract interacts with dopamine D3 receptors in a concentration-dependent manner.

Table 4. Interaction of Valerian extract with Human Dopamine D3 Receptors

Experiment No.	Concentration	N	% Inhibition
1	10 $\mu\text{g/mL}$	2	6
	100 $\mu\text{g/mL}$	2	13
	1000 $\mu\text{g/mL}$	2	77
2	31.3 $\mu\text{g/mL}$	4	4
	62.5 $\mu\text{g/mL}$	4	7
	125 $\mu\text{g/mL}$	4	6
	250 $\mu\text{g/mL}$	4	17
	500 $\mu\text{g/mL}$	4	24
	1000 $\mu\text{g/mL}$	4	49
	2000 $\mu\text{g/mL}$	4	82
3	100 $\mu\text{g/mL}$	2	24
	500 $\mu\text{g/mL}$	2	36

In order to identify compounds or class of compounds from valerian root extract that interact with the dopamine D3 receptor, Valerian was subjected to bioactivity-guided fractionation (see Figure 3). Valerian fractions were tested to determine their activity against the dopamine D3 receptor and active fractions were subjected to further sub-fractionation. The results from the testing of Valerian fractions and sub-fractions at various concentrations are summarized in Tables 5, 6, 7, and 8. These results indicate that several sub-fractions interact strongly with the receptor. Without being bound to any particular theory of action for the invention, the results of this example indicate that more than one compound may be responsible for the observed interaction of Valerian with the dopamine D3 receptor.

Table 5. Interaction of Valerian Fractions and Sub-fractions with Human Dopamine D3 Receptors

Sample	Description	% Inhibition	
		500 µg/mL	100 µg/mL
BKC-007-26-F0	Valerian extract	36	24
BKC-007-26-F1	CH ₂ Cl ₂ soluble portion of BKC-007-26-F0	108	86
BKC-007-26-F2	Butanol soluble portion of BKC-007-26-F0	37	8
BKC-007-26-F3	Water soluble portion of BKC-007-26-F0	-3	6
BKC-007-26-F4	Hexane soluble portion of BKC-007-26-F1	100	100
BKC-007-26-F5	CH ₂ Cl ₂ soluble portion of BKC-007-26-F1	65	55
BKC-007-26-F6	Methanol soluble portion of BKC-007-26-F1	64	-6
BKC-007-26-F7	Water elution of C18 column of BKC-007-26-F3	5	-16
BKC-007-26-F8	Organic elution of C18 column of BKC-007-26-F3	11	-20

Table 6. Interaction of Valerian Fractions and Sub-fractions with Human Dopamine D3 Receptors

Sample	Description	% Inhibition	
		100 µg/mL	20 µg/mL
KL-015-01-F1	CH ₂ Cl ₂ soluble portion of Valerian extract	88	33
KL-015-01-F4	Hexane soluble portion of KL-015-01-F1	104	26
KL-015-08-F1	Silica Gel VLC fraction of KL-015-01-F4	79	36
KL-015-08-F2	Silica Gel VLC fraction of KL-015-01-F4	91	46
KL-015-08-F3	Silica Gel VLC fraction of KL-015-01-F4	89	42
KL-015-08-F4	Silica Gel VLC fraction of KL-015-01-F4	23	16
KL-015-08-F5	Silica Gel VLC fraction of KL-015-01-F4	5	19
KL-015-08-F6	Silica Gel VLC fraction of KL-015-01-F4	9	2
KL-015-01-F5	CH ₂ Cl ₂ soluble portion of KL-015-01-F1	76	30
KL-015-03-F1	Silica Gel VLC fraction of KL-015-01-F5	22	22
KL-015-03-F2	Silica Gel VLC fraction of KL-015-01-F5	106	34
KL-015-03-F3	Silica Gel VLC fraction of KL-015-01-F5	113	42
KL-015-03-F4	Silica Gel VLC fraction of KL-015-01-F5	102	54
KL-015-03-F5	Silica Gel VLC fraction of KL-015-01-F5	56	18

Table 7. Interaction of Valerian Sub-fractions with Human Dopamine D3 Receptors

Sample	Description	% Inhibition		
		100 µg/mL	50 µg/mL	25 µg/mL
KL-015-01-F4	Hexane soluble portion of KL-015-01-F1	ND	58	22
KL-015-10-F1	Silica Gel Column Fraction of KL-015-03-F2	122	74	49
KL-015-14-F3	Silica Gel Column Fraction of KL-015-08-F1	126	92	85
KL-015-19-F1	Silica Gel Column Sub-Fraction of Pooled Active Fractions from Previous Steps	98	56	51
KL-015-19-F2	Silica Gel Column Sub-Fraction of Pooled Active Fractions from Previous Steps	19	14	13
KL-015-19-F3	Silica Gel Column Sub-Fraction of Pooled Active Fractions from Previous Steps	70	55	31
KL-015-19-F4	Silica Gel Column Sub-Fraction of Pooled Active Fractions from Previous Steps	86	44	22
KL-015-19-F5	Silica Gel Column Sub-Fraction of Pooled Active Fractions from Previous Steps	98	52	30
KL-015-19-F6	Silica Gel Column Sub-Fraction of Pooled Active Fractions from Previous Steps	88	53	41
KL-015-19-F7	Silica Gel Column Sub-Fraction of Pooled Active Fractions from Previous Steps	60	43	29
KL-015-19-F8	Silica Gel Column Sub-Fraction of Pooled Active Fractions from Previous Steps	48	22	24
<i>KL-015-039-F2</i>	Preparatory TLC Fraction of Pooled Active Fractions from Previous Steps	116	107	55

In summary, with regard to this example, it has been shown that Valerian inhibits ligand binding to the dopamine D3 receptor in a concentration dependent manner. Furthermore, the results of the bioactivity-guided fractionation indicate that there are compounds, or classes of compounds, from Valerian root extract that strongly interact with the dopamine D3 receptor.

EXAMPLE 4

BINDING POTENCY OF FURTHER PURIFIED SUB-FRACTIONS

Highly active sub-fractions were further purified and tested for their binding potency against the human dopamine D3 receptor, as outlined in Example 3. After full chemical characterization, active compounds were evaluated, as in Example 3. The results are shown in Table 8.

Table 8. Inhibition of Ligand Binding to the Human Dopamine D3 Receptor by Various Valerian Constituents

Sample	Description	N	Conc. (μ g/mL)	% Inhibition	Approximate EC ₅₀	
KL-015-040-F1	Acetoxyvalerenic Acid MW 292	2	200	16	> 200 μ g/mL	
		2	100	1		
		2	50	10		
		2	25	3		
		2	12.5	7		
		2	6.25	1		
KL-015-025-F2	Hydroxyvalerenic Acid MW 250	2	200	19	> 200 μ g/mL	
		2	100	17		
		2	50	0		
		2	25	-3		
		2	12.5	21		
		2	6.25	2		
KL-015-039-F1	Valerenic Acid MW 234	2	200	109	45 μ g/mL	192 μ M
		2	100	87		
		2	50	34		
		2	25	31		
		2	12.5	25		
		2	6.25	10		
VM-022-034-F1	10(14)- Aromadendren-4-ol MW 220	1	100	115	24.2 μ g/mL	110 μ M
		1	33.3	66		
		1	11.1	15		
		1	3.7	4		

Sample	Description	N	Conc. (μ g/mL)	% Inhibition	Approximate EC ₅₀
VM-022-034-F2	6, 10(14)-Guaiadien-4-ol	1	100	114	24.1 μ g/mL
	MW 220	1	33.3	66	
		1	11.1	15	
		1	3.7	5	
VM-022-034-F4	Valerenol	1	100	119	10.5 μ g/mL
	MW 220	1	33.3	88	
		1	11.1	45	
		1	3.7	25	
VM-022-022-F1	Degraded Valerenal	1	100	31	> 100 μ g/mL
		1	33.3	31	
		1	11.1	21	
		1	3.7	18	
VM-022-033-F1	Valerenal (VAL)	2	50	112	10.2 μ g/mL
	MW 218	2	25	94	
		2	12.5	49	
		2	6.25	26	
		2	3.13	25	
		2	1.56	7	
		2	0.78	8	
		2	0.39	10	
CB-001	Volatile Oil (VO)	1	100	104	19.5 μ g/mL
		1	33.3	55	
		1	11.1	32	
		1	3.7	21	
Combination	VA, AVA, VAL and VO (3:4:0.7:1); i.e. their ratio normally found in Valerian extracts	1	100	77	30.2 μ g/mL
		1	33.3	59	
		1	11.1	13	
		1	3.7	18	

The extracts and the specific compounds and classes of compounds described herein may be used to formulate medicaments using principles, and by techniques, well known to persons of ordinary skill of the art. These medicaments may be administered, by various techniques well known to persons of ordinary skill of the art, to hosts identified as afflicted with, or likely to be afflicted with, the conditions described herein.

The various articles and other references of the scientific and/or medical literature, and the U.S. and foreign patents and patent applications cited herein, including those listed below, are hereby incorporated by reference; each constitutes a part of the disclosure of this specification. Furthermore, while specific embodiments, working examples, and prophetic examples of the invention have been described in detail to illustrate the broad applicability and principles underlying the invention, it will be understood by those of skill in the art that the invention may be embodied otherwise without departing from such broad applicability and principles.

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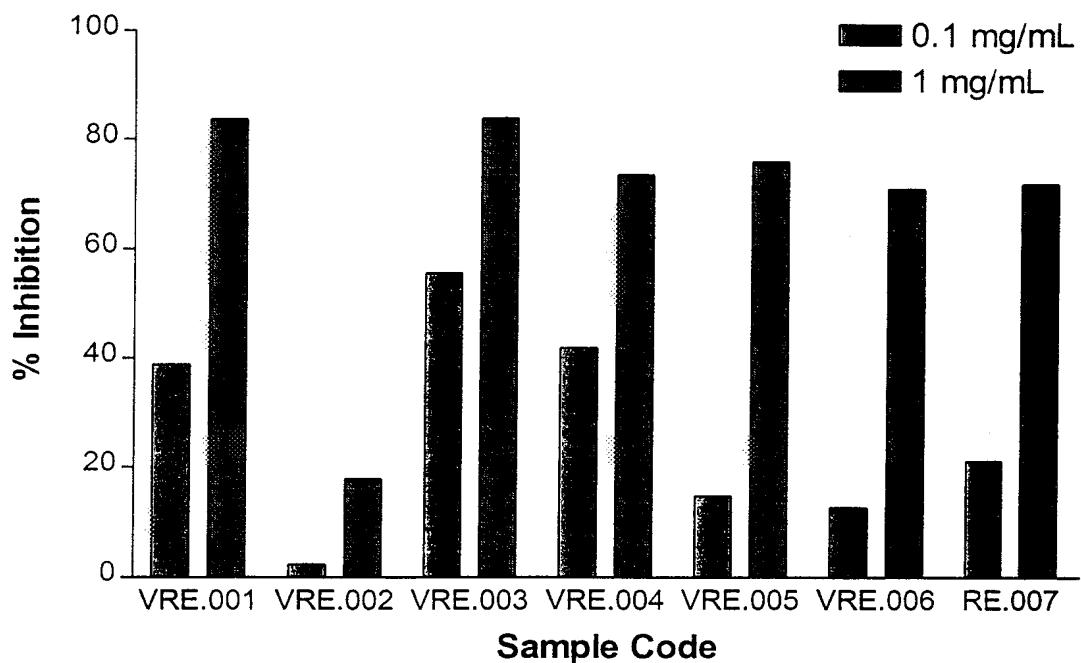
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WHAT IS CLAIMED IS:

1. A method of reducing the occurrence of at least one symptomology of Restless Leg Syndrome (RLS) and related disorders in a host, comprising the step of:
administering to the host a pharmaceutically effective amount of *Valeriana*.
2. The method of Claim 1, further comprising the step of identifying that the host is afflicted with Restless Leg Syndrome (RLS) or a related disorder.
3. The method of Claim 1, further comprising the step of identifying the occurrence of at least one symptomology of Restless Leg Syndrome (RLS) and related disorders in the host.
4. The method according to Claim 1, wherein said *Valeriana* is in the form of an extract.
5. The method according to Claim 4, wherein said *Valeriana* is an extract of *Valeriana officinalis*.
6. The method according to Claim 1, wherein said at least one symptomology is associated with insomnia in said host.
7. The method according to Claim 1, wherein said host is a mammal.
8. The method according to Claim 7, wherein said host is a human.
9. The method according to Claim 7, wherein said host is a selected from the group consisting of canines, felines, and rodents.
10. The method according to Claim 7, wherein said host is a mouse.
11. A method for diminishing undesired limb movements in a host, the method comprising the step of:
administering to the host a pharmaceutically effective amount of *Valeriana*.
12. The method of Claim 11, further comprising the step of identifying that the host suffers from undesired limb movements.
13. The method according to Claim 11, wherein said *Valeriana* is an extract.
14. The method according to Claim 11, wherein said *Valeriana* is an extract of *Valeriana officinalis*.
15. The method according to Claim 11, wherein said host is a mammal.
16. The method according to Claim 11, wherein said host is a selected from the group of canines, felines, and rodents.
17. The method according to Claim 15, wherein said host is a human.
18. The method according to Claim 15, wherein said host is a mouse.
19. A method of inhibiting at least one symptomology of Restless Leg Syndrome (RLS) and related disorders, comprising a step for:
administering to said individual a pharmaceutically effective amount a compound found in an extract of *Valeriana*
20. The method of Claim 19, wherein the compound is selected from the group consisting of 10(14)-Aromadendren-4-ol, 6,10(14)-Guaiadien-4-ol, Valerenal, Valerenol, Valerenic acid, Acetoxyvalerenic acid, Hydroxyvalerenic acid, mimetics thereof, and combinations thereof.
21. The method according to Claims 19, wherein said individual is a mammal.

22. The method according to Claims 21, wherein said individual is selected from the group of canines, felines, and rodents.
23. The method according to Claims 21, wherein said individual is a human.
24. The method according to Claims 21, wherein said individual is a rodent.
25. Use of a pharmaceutically effective amount of *Valeriana* for the treatment of at least one symptomology of Restless Leg Syndrome (RLS) and related disorders in a host.
26. Use of a pharmaceutically effective amount of *Valeriana* for the preparation of a medicament for the treatment of Restless Leg Syndrome (RLS) in a host.
27. Use of a pharmaceutically effective amount of *Valeriana* for the preparation of a medicament for the treatment of undesired limb movements in a host.
28. The use of Claim 25, 26 or 27, wherein said host is a mammal.
29. The use of Claim 25, 26 or 27, wherein said host is a human.
30. The use of Claim 25, 26 or 27, wherein said host is a selected from the group consisting of canines, felines, and rodents.
31. The use of Claim 25, 26 or 27, wherein said host is a mouse.
32. The use of Claim 25, 26 or 27, wherein said *Valeriana* is in the form of an extract.
33. The use of Claim 25, 26 or 27, wherein said *Valeriana* is an extract of *Valeriana officinalis*.
34. The use of Claim 25, wherein said at least one symptomology is associated with insomnia in said host.
35. A method of reducing the occurrence of at least one symptomology of Restless Leg Syndrome (RLS) and related disorders, substantially as described herein.
36. Use of a pharmaceutically effective amount of *Valeriana* substantially as described herein.

FIG. 1



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FIG. 2

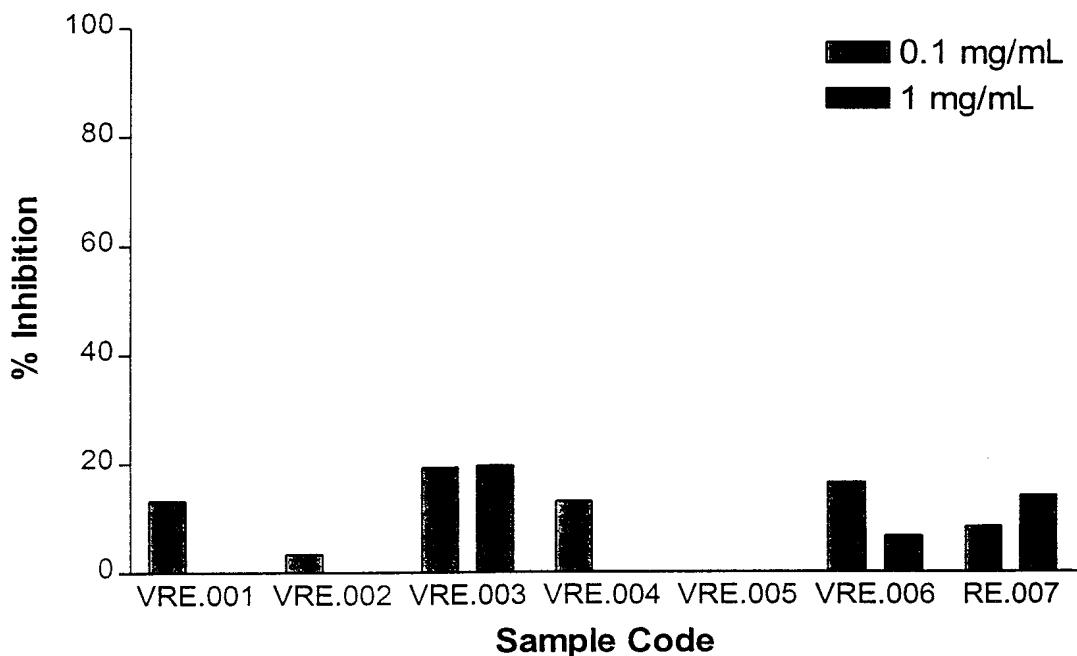


FIG. 3

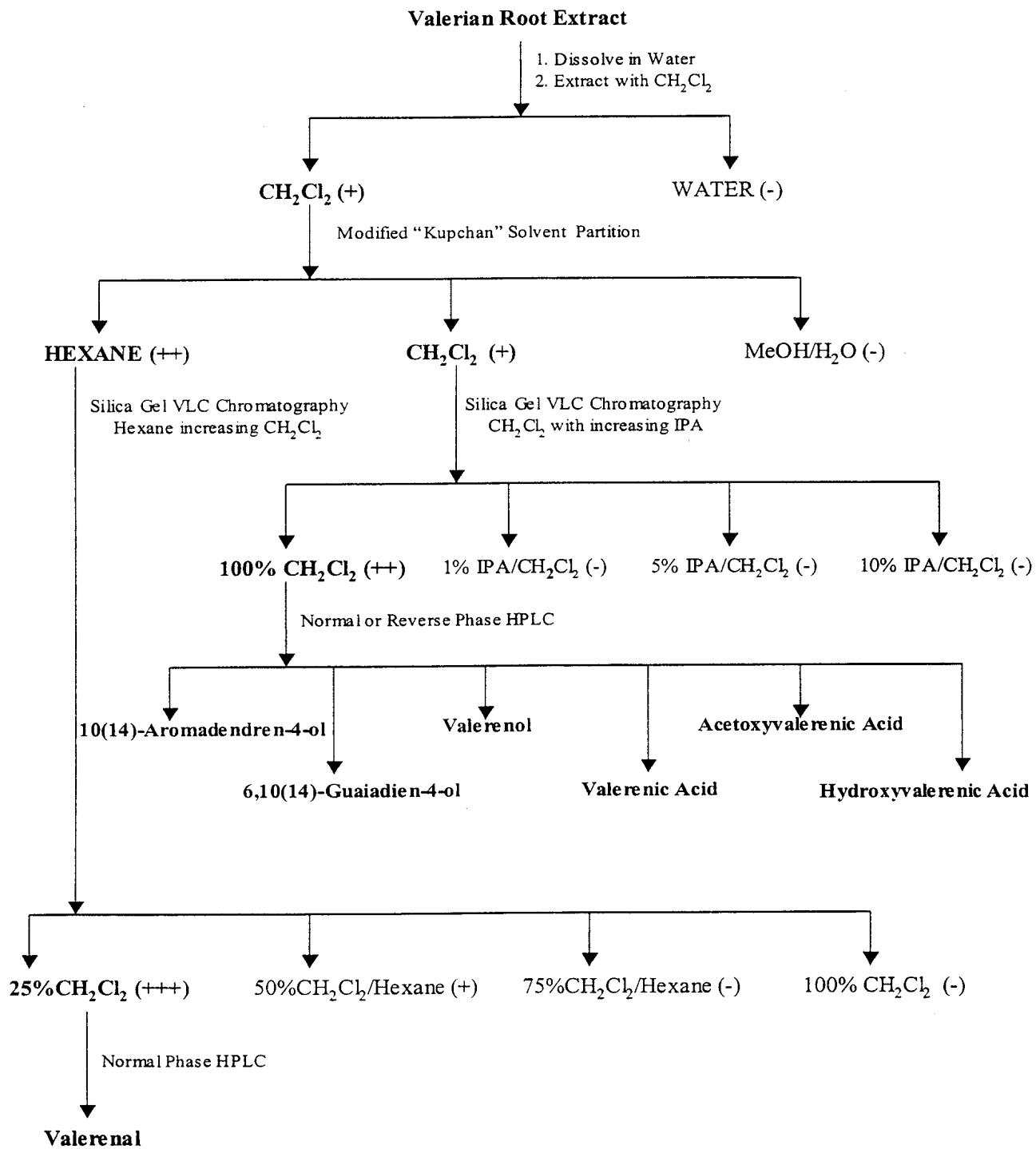
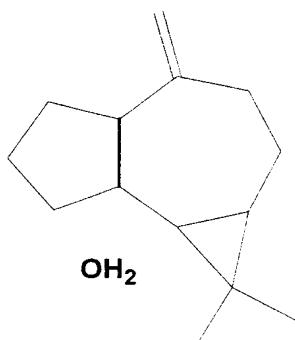
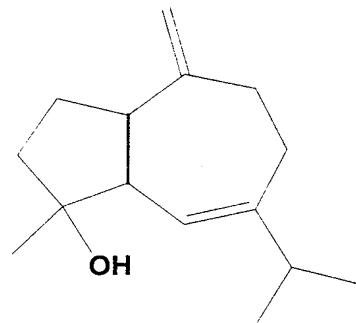


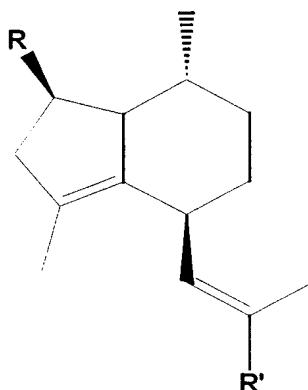
Fig. 4

DOPAMINE D3 ACTIVE COMPOUNDS

10(14)-Aromadendren-4-ol



6,10(14)-Guaiadien-4-ol



COMPOUND	R GROUP	R' GROUP
Valerenal	-H	-CHO
Valerenol	-H	-CH ₂ OH
Valerenic Acid	-H	-CO ₂ H
Acetoxyvalerenic Acid	-OAc	-CO ₂ H
Hydroxyvalerenic Acid	-OH	-CO ₂ H

Inhibition of Ligand Binding to the Human Dopamine D3 Receptor by Various Compounds Isolated from Valerian

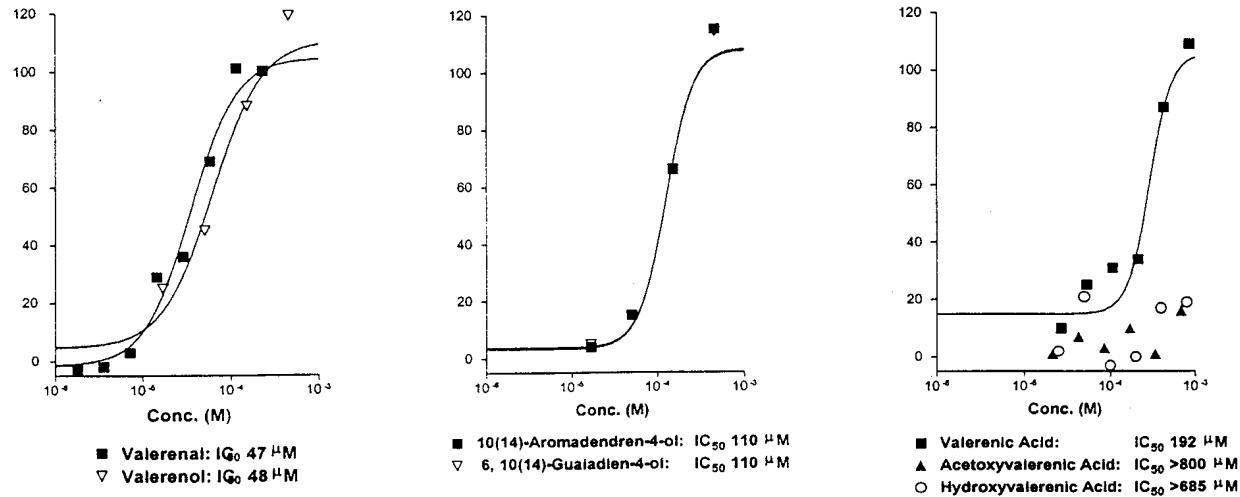


FIG. 5

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/07998

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K35/78 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, CHEM ABS Data, BIOSIS, EMBASE, PHARMAPROJECTS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>MORAZZONI P., ET AL.: "Valeriana officinalis: traditional use and recent evaluation of activity" FITOTERAPIA, vol. 66, no. 2, 1995, pages 99-112, XP002049843 italy *cf. summary, page 106, 3rd para., page 109, "clinical trials", first two paras.*</p> <p>---</p>	1-36
Y	<p>WO 98 08498 A (ARTMAN LINDA D ;NPS PHARMA INC (US); BALANDRIN MANUEL F (US)) 5 March 1998 (1998-03-05) *cf. abstract, page 2, last para. bridging with page 3, lines 1-8, page 4, last para. with page 5, lines 1-24*</p> <p>---</p> <p style="text-align: center;">-/-</p>	1-36

Further documents are listed in the continuation of box C.

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Stoltner, A

INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>MENNINI T., ET AL.: "In vitro study on the interaction of extracts and pure compounds from <i>valeriana officinalis</i> roots with GABA, Benzodiazepine and Barbiturate receptors in rat brain" FITOTERAPIA, vol. 64, no. 4, 1993, pages 291-300, XP000916631 *cf. summary, page 292, last para., page 299, the last 12 lines from the foot*</p> <p>---</p>	1-36
A	<p>WO 97 39355 A (PHARMAPRINT INC ;UNIV SOUTHERN CALIFORNIA (US); KHWAJA TASNEEM A () 23 October 1997 (1997-10-23) *cf. pp. 190, lines 1-27, page 191 bridging with page 192, first para.*</p> <p>-----</p>	1-36

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/07998

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		US 6039950	A	21-03-2000
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